Microchips as Controlled Drug-Delivery Devices

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Controlled-release systems are common in a number of product areas, including foods, cosmetics, pesticides, and paper. Microencapsulated systems, for example, are used for the release of flavors and vitamins in foods, fragrances in perfumes, and inks in carbonless copy paper. Controlled-release systems for drug delivery first appeared in the 1960s and 1970s. In the past three decades, the number and variety of controlled release systems for drug-delivery applications has increased dramatically. Many of these use polymers having particular physical or chemical characteristics such as biodegradability, biocompatibility, or responsiveness to pH or temperature changes. However, recent advances in the field of microfabrication have created the possibility of a new class of controlled-release systems for drug delivery, namely, that of small, programmable devices. Their small size, potential for integration with microelectronics, and ability to store and release chemicals on demand could make controlled-release microchips useful in a number of areas, including medical diagnostics, analytical chemistry, chemical detection, industrial process monitoring and control, combinatorial chemistry, microbiology, and fragrance delivery. More importantly, drug-delivery microchips resulting from this convergence of controlled release and microfabrication technologies may provide new treatment options to clinicians in their fight against disease.

Keywords: controlled release · drug delivery · drug research · microchips · microreactors

1. Introduction

Microelectronic devices have become an integral part of our lives. They are present in our automobiles, cellular phones, and personal computers. This review examines an emerging new field: the application of microfabrication technologies to the development of devices for the controlled release of chemicals, including drugs. To provide the proper background for understanding this new field, we begin with an overview of the field of controlled release and then briefly discuss relevant work from the field of microfabrication. The remainder of the article reviews our recent work on the development of controlled-release microchips for chemical- and drug-delivery applications.

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2. Overview of Controlled Release

Controlled release, as used in this review, refers to materials or devices for controlling the release time of a chemical, the release rate, or both. Controlled release has proved useful in areas such as foods, cosmetics, and pesticides,[1] but it has had its largest impact in the field of drug delivery.[2]

The method by which a drug is delivered can have a significant effect on its therapeutic efficacy.[3] Some drugs have an optimum range of concentrations within which the maximum therapeutic benefit is derived. Drug concentrations above or below this range can be toxic or produce no therapeutic benefit. Conventional drug-delivery systems such as tablets or injections typically result in a drug-delivery profile that is initially marked by a sharp increase in concentration to a peak above the therapeutic range. Then, there is a relatively rapid decrease in concentration until the drug falls below the therapeutic range. Therefore, the time spent in the optimum concentration range may be short

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(Figure 1 a). Sleeping pills are a good example for illustrating the importance of drug concentration. If the drug concentration is below the therapeutic range, enhancement of sleep is not observed. If the drug concentration is above the therapeutic range, potentially fatal toxicity may be encountered. Therefore, the ideal concentration profile, in some cases, would reside in the therapeutic range and be nearly independent of time (Figure 1 a).

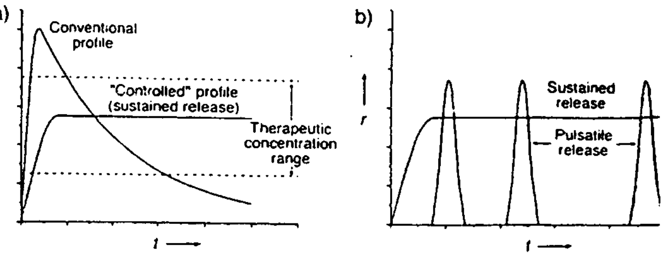

Figure 1. a) Exemplary concentration c vs. time t profiles for conventional and controlled-release drug-delivery devices. The controlled release profile here is characteristic of sustained (or continuous) release. b) Exemplary release rate r vs. time profiles demonstrating the difference between sustained (or continuous) release and pulsatile release.

2.1. Sustained Release

The field of controlled release initially focused on achieving a sustained (or continuous) release of drug over an extended

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period of time (Figure 1 b) with minimal influence by outside factors such as pH.[4] Much of this work involved polymers that released the drug at a nearly constant rate due to diffusion out of the polymer or by degradation of the polymer over time. These controlled-release systems may be of a macro- or microscopic size and exist in a number of different forms, such as oral tablets, polymer implants (rods, wafers, or pellets), and polymer microspheres. Two examples of commercially available polymeric devices for constant drug release include Gliadel[5] (implantable polyanhydride wafers that release carmustine for the treatment of malignant brain tumors at a nearly constant rate as the polymer degrades) and Lupron Depot[6] (injectable polymer microspheres, for treatment of endometriosis, precocious puberty, or for the nearly constant release of LHRH analogues for prostate cancer therapy).

Transdermal delivery is another method that achieves sustained release of drugs. It has proved successful for small lipophilic drug molecules such as scopolamine (motion sickness), fentanyl (pain), clonidine (hypertension), estradiol (hormone replacement), testosterone (impotence), nicotine (smoking cessation), and nitroglycerin (angina).[2, 7] A major advantage of transdermal delivery is that first-pass metabolism of the administered drug by the liver is reduced.[7b] However, there is typically a lag time between the application to the skin and the establishment of a stable concentration of the drug in the bloodstream, and only a limited number of drugs can penetrate the skin at rates fast enough to reach a therapeutic steady-state concentration in the bloodstream without chemical enhancers or external stimuli such as ultrasound.[8]

2.2. Pulsatile Release

The examples presented in Section 2.1 are designed to release drugs at a nearly constant rate. In numerous cases, however, sustained release is not the optimal method of drug delivery. Instead, delivery of pulses of drug at variable time intervals is the preferred method (Figure 1b) and is commonly referred to as pulsatile release. This delivery method works better in certain cases because it closely mimics the way in which the human body naturally produces some compounds. Insulin is a well-known example of a compound secreted by the body in a pulsatile manner.[9] Another example of compounds produced by the body in a pulsatile or periodic manner are the hormones of the anterior pituitary gland (adenohypophysis), for example gonadotropin and growth hormone, which are important in regulating reproduction and growth, respectively. Many compounds and environmental factors can stimulate or inhibit the production of these hormones. However, compounds secreted by the hypothalamus, called releasing factors or hormones, play a primary role in the regulation of adenohypophysial hormones. For example, women suffering from gonadotropin releasing hormone (GnRH) deficiency may not ovulate normally, making it difficult to conceive a child. Growth hormone releasing hormone (GHRH) deficiency in children may lead to dwarfism. Pulsatile administration of GnRH and GHRH can help reduce the severity of these deficiencies.[10] In fact, continuous adminstration of GnRH results in desensitization of GnRH receptors on the pituitary gland and may actually suppress the release of gonadotropins.[11]

Much previous work on methods of achieving pulsatile release focused on developing polymers that respond to specific stimuli:[12] changes in electric[13] or magnetic[14] fields, exposure to ultrasound,[14b, 15] light,[16] enzymes,[17] changes in pH[18] or temperature,[19] or molecules present in the human body, including antigens.[20] Transdermal delivery, typically a route for sustained delivery, can be modified to produce a more pulsatile release pattern in the presence of ultrasound[8] or voltage pulses (high voltage: electroporation, low voltage: iontophoresis).[21] Pulsatile release systems can be externally regulated (open-loop) or self-regulated (closed-loop).[22] A polymer implant that releases a drug when an oscillating magnetic field is applied is an example of an externally regulated system,[23] while a system that releases drug in response to antigens in the body is an example of self-regulation.[20] An example of oral and implantable polymer devices capable of delivering pulses of drug without the use of an external stimulus are those fabricated by Three Dimensional Printing. They are based on the controlled microstructure of the polymer matrix and release drugs at specified times as determined by the permeability of the polymer and the position of the drug in the device.[24]

An alternative method of pulsatile release involves the use of pumps and catheters. Pumps work well for both sustained and pulsatile release and can be programmed to deliver pulses of drug solutions to a patient through a catheter at different times. In fact, one of the current methods for treating GnRH deficiency in women involves wearing a pump (about the size of an adult fist) on a belt with a subcutaneous or intravenous catheter.[25] The pump delivers a pulse of a solution containing 5 µg of GnRH every 90 min for several weeks to months. However, some external pump and catheter systems can be inconvenient and uncomfortable, can limit the patient's mobility, can be expensive, and may result in irritation or infections at the catheter site. Completely implantable pumps, developed for diabetes, oncology, or analgesia,[26] for example, may improve patient mobility and reduce infections by eliminating transcutaneous catheters, but they may still be hampered by their size, cost, ability to deliver only drugs in solution, and the limited stability of some drugs in solution at 37 °C.

3. Overview of Microfabrication Technology

Microfabrication can be generally defined as the production of microscale features in or on a material by techniques such as deposition, etching, micromolding,[27] along with patterning techniques such as photolithography[27a-c] or microcontact printing.[28] Microfabrication has traditionally been used to produce integrated circuits for microelectronic devices such as computer microprocessors. However, microfabrication has been used increasingly to produce microscale devices whose primary function is mechanical, chemical, or optical in nature. Such devices include microreactors, micro-

pumps, accelerometers, and micromirrors, and are commonly referred to as microelectromechanical systems (MEMS). MEMS are commonly made with silicon and microelectronic processing techniques. However, MEMS can also be made from plastics, glass, metals, or ceramics by processes such as stamping, casting, molding, and laser ablation.

MEMS have found use in a number of fields. Two notable examples are the fabrication of nozzles for ink-jet printers[29] and accelerometers for automotive applications.[30] More recent advances in MEMS include the development of microreactors for the production of chemicals[31] and microturbine engines for aerospace applications.[32] For the purposes of this review, microfabricated devices for biological applications can generally be classified as microfluidic devices and nonmicrofluidic devices.

3.1. Microfluidic Devices

Microfluidics is an area of microfabrication that focuses on the miniaturization of fluid-handling systems such as pumps, valves, and flow channels. The concept of fabricating entire chemical labs-on-a-chip or miniaturized total analysis systems (μTAS) that include pumps, valves, mixers, reactors, and separators has recently generated much interest.[33] The demand for such systems has resulted in the development of numerous microfluidic components such as micropumps and microvalves.[34] Micropumps can be based on moving parts such as diaphragms or piezoelectric components that mechanically pump liquids[35] or they can move ionic fluids by using electric fields (i.e. electroosmotic pumping).[36] Microfabricated valves with pneumatic[37] or thermoelectric[38] actuators can operate reversibly. Irreversible valves based on electrochemical actuation have also been suggested.[39]

Recent interest in microfluidics for biological applications has focused largely on developing microsystems for chemical[33c, 40] or DNA[33b,d, 41] analysis. Other areas where microfluidic devices have been utilized include combinatorial chemistry,[33b] bioassays,[42] and capillary electrophoresis systems. For example, various methods of capillary electrophoresis on polydimethylsiloxane and fused silica microdevices have been used to separate DNA fragments,[43] oligonucleotides,[44] polymerase chain reaction (PCR) products,[45, 46] single DNA molecules,[43a, 47] and single-[41e] and double-stranded[48] DNA. Capillary electrophoresis on microdevices has also been used for DNA genotyping[49] and the separation of neurotransmitters,[45] amino acids,[50] peptides,[43a] insulin, and lysozyme.[43b]

3.2. Nonmicrofluidic Devices

Nonmicrofluidic devices for biological applications do not involve the pumping or controlled movement of fluids and include many biosensors and some "DNA chips". Biosensors can be manufactured from silicon by using semiconductor processes, but their fabrication often involves at least one unconventional step to produce surface features or coat the sensor with a biologically or chemically active compound.[51] Similarly, DNA chips use immobilized materials on the device surface to identify genetic material or other chemicals.[52] Over the last several years, DNA chips have become popular with pharmaceutical companies for high-throughput drug screening and combinatorial chemistry.

The use of microfabrication technology in biological applications has grown tremendously in recent years. However, microfabrication has found limited use in the fields of controlled release and drug delivery. One could envision using microfluidic devices to achieve drug release, but the potential limitations of delivering only liquid drug formulations, the instability of certain drugs in solution, the complexity of some fabrication schemes, and the presence of moving parts that are subject to breakdown may present obstacles to their clinical and commercial use. As a result, the field of controlled release has yet to take full advantage of microfabrication technology.

4. Controlled Release Microchips

The ultimate goal of our work was to develop a microfabricated device with the ability to store and release multiple chemical substances on demand by a mechanism devoid of moving parts.

4.1. Theory of Operation

Figure 2 shows a model embodiment of a controlled-release microchip consisting of an array of reservoirs that extend through an electrolyte-impermeable substrate. Each reservoir is sealed at one end by a thin membrane of material that serves as an anode in an electrochemical reaction and dissolves when an electric potential is applied to it in an electrolyte. There must be at least one other electrode on the device surface to serve as a cathode in the electrochemical reaction. The cathode can be made of any conductive material but is usually made of the same material as the anodes to simplify fabrication procedures. In addition, any number of cathodes can be included on a microchip, and they can be of any shape or size to suit the electrode design desired for a particular application. The reservoirs are filled through the open end with the chemical to be released. The open ends of the reservoirs are then sealed with a waterproof material.

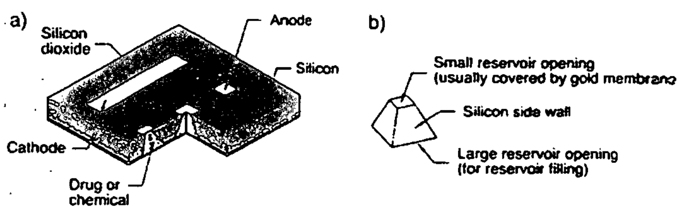

Figure 2. A schematic of a typical controlled-release microchip. a) Cut away section showing anodes, cathodes, and reservoirs. b) shape of an individual reservoir (see Section 4.2 for typical dimensions).

The device is submerged in an electrolyte containing ions that form a soluble complex with the anode material in its ionic form. An electric potential is applied to an anode membrane when release from its corresponding reservoir is desired. This causes oxidation of the anode material and formation of the soluble complex with the electrolyte ions. The complex then dissolves in the electrolyte, and the membrane disappears. Figure 3 shows the principle of operation schematically. The chemical in the newly opened reservoir is now exposed to the surrounding electrolyte and is free to dissolve in the electrolyte and diffuse out of the reservoir.

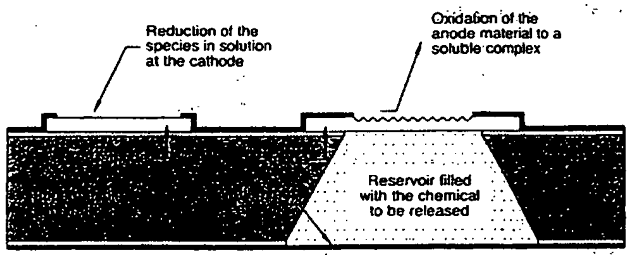

Figure 3. A cross section of a typical controlled-release microchip illustrating the principle of the electrochemical reservoir opening mechanism. The materials used in prototype microchips are described in Section 4.2.

4.2. Experimental Prototype Specifications

Four-inch-diameter silicon wafers were used as the initial model substrate material for the prototype controlled-release microchips. The prototype was a 17 × 17 mm square silicon device containing thirty-four reservoirs that extended completely through the silicon. The reservoirs were square pyramidal in shape (see Figure 2b) due to the potassium hydroxide etching method used to fabricate them. The small reservoir opening was approximately 50 × 50 μm, and the large opening approximately 480 × 480 μm. The thickness of the silicon substrate varied between 295 and 315 μm, so that each reservoir had a volume of approximately 25 nL. Each reservoir was sealed at the small end by a 0.2–0.3-μm gold membrane that served as an anode in an electrochemical reaction. Three thin-film gold cathodes were placed at different intervals across the surface of the device. Some portions of the gold anodes and cathodes were covered by a 0.4–0.6-μm silicon dioxide film to prevent corrosion in those areas during the application of an electric potential. The prototype microchip shown in Figure 4 had only three cathodes for thirty-four anodes. Twenty-one such prototype microchips can be fabricated on one four-inch silicon wafer.

The size of the prototype device was selected strictly for ease of handling during release experiments and compatibility with commercially available device packaging. However, devices are not restricted to that size and could be made much larger or smaller (< 2 mm), depending on the particular application. A device of the size used in these studies (17 × 17 mm) can accommodate over 1000 reservoirs.

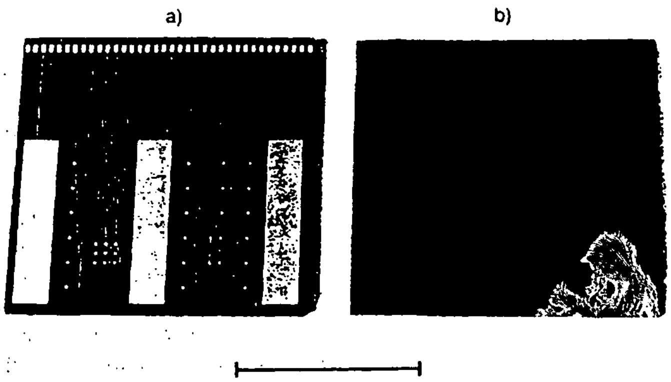

Figure 4. Photographs of a prototype microchip. a) The electrode-containing front side, b) the back side with the openings for filling the reservoirs. (Scale bar: 10 mm; photographs by Paul Horwitz.)

4.3. Selection of the Membrane Material

Selection of the proper membrane material is critical for the reliable operation of controlled-release microchips. A key requirement for the membrane material is that it should remain stable in the solution in the absence of an applied electric potential to prevent premature release of the chemical from the microchip. The membrane material must also be able to dissolve quickly and selectively when a specific electric potential is applied to it. However, selecting a material possessing both of these qualities is difficult because biological fluids contain a small amount of dissolved oxygen and chloride ions, which cause many metals to corrode spontaneously.

Gold was selected as the initial model membrane and electrode material primarily due to its unique electrochemical properties. Gold has long been considered a noble metal. It is easily deposited and patterned, has a low reactivity with other substances, and resists spontaneous corrosion in most aqueous solutions over the entire pH range. The fact that the gold surface remains clean (i.e., the native oxide layer on a gold surface, if present, is very thin) and does not corrode in most environments led to its widespread use in jewelry, currency, medical implants, and microelectronic devices. Pourbaix diagrams indicate the thermodynamically stable species in a solution at any combination of applied potential and solution pH. A computer-generated[53] Pourbaix diagram for gold in aqueous solutions free from complexing substances is shown in Figure 5. The diagram indicates that gold, when no electric potential is applied, is immune to corrosion over the entire domain of water stability (the area between the dotted lines). The species in areas delineated by solid lines are the thermodynamically stable, solid species at each combination of applied potential and solution pH.

The presence of a small amount of chloride ions in solution creates an electric potential/pH region that thermodynamically favors the formation of water-soluble chlorogold complexes.[54] The presence of a complexing substance such as chloride can change the Pourbaix diagram for gold in aqueous solutions (Figure 6a). However, thermodynamics does not tell the whole story. It is also important to look at the kinetics of

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